# Challenges and the future of 3D bioprinting.

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## Editorial

3-dimensional (3D) printing also called additive manufacturing (AM) has found applications in a variety of industries including construction, food, aerospace and manufacturing. Recently, it has gained interest in medicine and tissue engineering applications as well. 3D bioprinting involves creating structures layer-by-layer by depositing a bioink which is a mixture of cells, biocompatible polymers and biomolecules. 3D bioprinting is a path to generate patient specific tissues and organs that when the patient needs a donor and in the times of donor scarcity, it can be a solution to resort [1-4].

Using 3D bioprinting, researchers were able to construct several different tissues including bone, skin, cartilage, muscle and neural. 3D bioprinting has great advantages in building scaffolds over conventional approaches that it can position the cells precisely. The desired architecture is fed into a computer aided file (CAD) through 3D imaging and printed layer by layer with predetermined x, y and z coordinates. For example, McAlpine et al. [5] used 3D bioprinting technology to generate complex anatomical structures with the guidance of 3D scanned images of a rat's bifurcating sciatic nerve. The complex structure of the nerve pathways was fed into a CAD file and then, they built the 3D printed hollow silicone which was a replica of the in vivo nerve pathway. Brain is a 3D complex tissue that is composed of several layers. The neural network between layers brings the additional complexity that make it difficult to understand how brain works. Wallace et al. [6] developed 3D brain-like structures that were created in layer by layer by 3D bioprinting. They built in each layer distinct cell populations and after several days of culture confocal microscopy images demonstrated the axonal penetration between layers that the structure was mimicking the in vivo case better than 2D models *in vitro*.

Despite the successful studies and reported outstanding research efforts, the path to fully built a 3D bioprinted organ has yet to be accomplished and there are several challenges to be solved to further advance this exciting research theme. The bioprinter technology needs to increase resolution and speed and should be compatible with a wider spectrum of biocompatible materials. Higher resolution will enable better interaction and control in 3D microenvironment. Currently, printing process is slow so speeding up building the architectures is essential. To reach to a commercially acceptable level that is being able to mass produce requires faster printing and scaling up the process. Biomaterials are undoubtedly the primary limitation for this technology. We are limited to several biocompatible synthetic and natural polymers. Synthetic materials provide the mechanical strength and natural polymers are more favorable for cell attachment, proliferation and differentiation. Therefore, a blend of these polymers is needed in addition to being compatible with the printing technology. Biomaterial's viscosity and crosslinking mechanism determines its printability. The choice of cell source also determines the success of the printed construct. Stem cells are multipotent that can turn into multiple different cell types and can build different tissues. Embryonic and induced pluripotent stem cells can turn into any cell type. The type chosen determines the route and requirements to differentiation and their interaction with the scaffold material. Clearly, advancements in controlling cellular fate has a direct effect on the success of building viable 3D tissue constructs [7]. Another fundamental issue is the vasculature of the printed construct [8]. *In vivo* 3D tissue is constantly fed by oxygen and nutrients, and the waste products are removed from the microenvironment with the help of the vasculature. Using a 3D bioprinter, if a thick 3D tissue is constructed, then this structure also needs a vascular system so that cells receive oxygen and nutrients and waste products and carbon dioxide is removed from the environment. Diffusion by itself will only work up to 150 micrometer thickness. Beyond this thickness, tissue will not develop properly, or necrosis will occur. This vasculature should be integrated in the construct in the early stages so that endothelium grows properly and functions in homeostatic balance. One approach is to build vasculature during bioprinting either with biodegradable or synthetic polymers that eventually leads to a vascularized tissue [9]. The problem is that however vessel diameters are determined by nozzle and currently are too large for an efficient vasculature. Another approach is to mix angiogenic factors in the bioink that within the construct a vasculature is formed. Forming a vascular system with angiogenic factors is a complex process and difficult to control. Therefore, more efforts are being demanded to solve this challenge.

In addition to technical challenges, there are ethical problems involved in 3D bioprinting as in many other aspects of bioengineering. These are equality, safety and human enhancement [10]. Equality refers to whether the rich and the poor are going to have equal opportunities to access 3D bioprinting. Personalized medicine will be costly and how will the poor afford it? Is this technology then going to be available for only those can afford?

Safety is interested in if this new technology going to be safe for humans and whether the responsible personnel are going to be trained sufficiently to handle it? Lastly, are we going to use this novel technology to build better humans? Replace some organs with a new one that supersedes the earlier? For example, are we going to have a better muscle tissue that does not fatigue easily? These questions and as discussed earlier, technical concerns will need to be addressed down the road before this novel technology becomes fully operational and effective.

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